Short Report

PTEN mosaicism with features of Cowden syndrome


We present the first known case of somatic PTEN mosaicism causing features of Cowден syndrome (CS) and inheritance in the subsequent generation. A 20-year-old woman presented for genetics evaluation with multiple ganglioneuromas of the colon. On examination, she was found to have a thyroid goiter, macrocephaly, and tongue papules, all suggestive of CS. However, her reported family history was not suspicious for CS. A deleterious PTEN mutation was identified in blood lymphocytes, 966A>G, 967delA. Genetic testing was recommended for her parents. Her 48-year-old father was referred for evaluation and was found to have macrocephaly and a history of Hashimoto’s thyroiditis, but no other features of CS. Site-specific genetic testing carried out on blood lymphocytes showed mosaicism for the same PTEN mutation identified in his daughter. Identifying PTEN mosaicism in the proband’s father had significant implications for the risk assessment/genetic testing plan for the rest of his family. His result also provides impetus for somatic mosaicism in a parent to be considered when a de novo PTEN mutation is suspected.

Conflict of interest
The authors declare that they have no conflict of interest.

Symptomatic somatic mosaicism is a rare occurrence in hereditary cancer syndromes, but has been reported in conditions such as familial adenomatous polyposis and neurofibromatosis types 1 and 2 (1–3). To the authors’ knowledge, somatic mosaicism resulting in features of Cowden syndrome (CS) has not been previously described. CS is an autosomal dominant condition caused by germline mutations in the PTEN gene. Germline PTEN mutations lead to a spectrum of disorders, including CS and Bannayan–Riley–Ruvalcaba syndrome, collectively called PTEN hamartoma tumor syndrome (PHTS) (4). CS is characterized by characteristic mucocutaneous skin findings in greater than 95% of cases, multiple benign hamartomatous polyps and tumors in addition to increased risks for breast, thyroid, endometrial, colon, and renal cell carcinomas (5, 6). Here, we describe the clinical and molecular characteristics of the first reported case of somatic PTEN mutation mosaicism resulting in features of CS.

Case presentation
A 20-year-old woman presented with a long history of stomach problems and abdominal discomfort. An esophagogastroduodenoscopy (EGD) and colonoscopy were therefore performed. The EGD revealed diffuse gastritis and duodenal biopsies showed mild villous blunting suggestive of celiac disease. Colonoscopy showed numerous rectal polyps, a large abnormal fold in the sigmoid colon, three ascending colon polyps, and one polyp on the ileocecal valve. The rectal polyps and abnormal sigmoid fold were ganglioneuromas. Pathology of the ascending colon polyps showed inflammatory polyps, whereas the ileocecal polyp was consistent with mucosal neuma. A capsule endoscopy was performed to look for small intestinal polyps and revealed mild scalloping in the proximal small intestine and an area of thickened-appearing mucosa in the distal small bowel, which was suggestive of a polyp or inflammation. Because of her multiple colorectal polyps, she
was referred for genetics evaluation. During her genetics appointment, physical examination revealed macrocephaly (head circumference of 59.5 cm), thyroid goiter, and tongue papules (Fig. 1).

Given the patient’s tongue papules, macrocephaly, and multiple ganglioneuromas, CS was strongly suspected. PTEN genetic testing was performed and a deleterious mutation was identified in her blood lymphocytes, 966A>G, 967delA. The patient was sent to endocrinology and a partial thyroidectomy was performed because of her multinodular goiter. A total body skin examination was also performed by a dermatologist experienced with CS and a firm/gritty papule located on her forehead was identified (not biopsied), which was suggestive of a trichilemmoma (Fig. 2), but no other dermatological findings suspicious of CS were noted except for the previously mentioned papillomatous papules on her tongue.

As per the patient’s reported family history, none of her siblings, parents, or maternal/paternal aunts and uncles had been diagnosed with cancer. Her maternal grandmother had been diagnosed with endometrial cancer at the age of 60, but had no history of colon polyps. Her paternal grandfather was reported to have had melanoma in his late 70s. Among the patient’s four siblings, one sister (age 22) reportedly had a thyroid goiter; one brother (age 8) was reported to have a larger than average head circumference, but no other features of PHTS.

Site-specific testing was recommended for her parents. The proband’s 48-year-old father was seen in genetics and was found to be macrocephalic (head circumference of 61 cm). Other than Hashimoto’s thyroiditis, he had no other significant health concerns and had not yet had a colonoscopy. No mucocutaneous lesions suggestive of CS were identified.

Result

The proband’s father was found to be mosaic for the 966A>G, 967delA PTEN mutation in blood lymphocytes. Sequencing showed the mutation to be present in less than 10% of the total sequence analyzed using peak height ratios (Fig. 3).

Discussion

Apparently de novo PTEN mutations have been reported in at least 10% of PHTS probands (4). However, it is unknown if these cases of de novo PHTS are due to somatic or germline PTEN mosaicism in a parent (4, 7). The proband’s father represents the first known reported case of somatic PTEN mutation mosaicism,
which resulted in mild CS features in him and PHTS in his daughter. Our proband had a history of multiple medical concerns, but no significant family history of cancer. If she had not presented with gastrointestinal concerns prompting colonoscopy and referral for genetic counseling, her eventual diagnosis of PHTS may have been further delayed, with potentially greater consequences to her health. Although PHTS is certainly rare, her presentation encourages physicians and other health care providers to be aware that unusual clinical findings can suggest a hereditary syndrome and warrant genetic evaluation.

The identification of mosaicism in the proband’s father has important implications for their family members. It is highly unlikely that the father’s siblings or parents are at risk for the mutation, and therefore genetic testing for the familial mutation in them is not necessary. As the father has over five siblings, this will save the family from unnecessary cost, time, and worry. PTEN testing for our proband’s four siblings is still warranted. If PTEN mutation mosaicism had not been identified in our patient’s father through blood lymphocyte testing, site-specific mutation testing in another tissue type (skin biopsy) would be warranted given his mild CS features (macrocephaly).

Because of the father’s mosaic status, the level of mutation distribution throughout his body is unclear. The mosaicism likely explains the variable phenotype between father and daughter. His mosaic PTEN status may also result in lower cancer risks compared to individuals with a germline PTEN mutation. Given this uncertainty, we have recommended that he may follow the standard cancer screening recommendations for men with CS, including increased screening for colon cancer, thyroid cancer, and dermatologic findings (8).

These results reinforce the importance of site-specific genetic testing for the parents and siblings of individuals with molecularly confirmed hereditary cancer syndromes, even when a de novo mutation is suspected. These results also show how careful laboratory analyses can detect low-level mosaicism and reporting of such a result can be helpful in determining the testing strategy for extended family members.

Acknowledgement
We acknowledge the use of core facilities supported by P30 CA042014 awarded to Huntsman Cancer Institute.

References